Hanover, John A. 2009

Dr. John A. Hanover Oral History 2009

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NCI Laboratory of Molecular Biology

Oral History Project

Interview with Dr. John A. Hanover

Conducted on January 14, 2009, by Jason Gart

JG: My name is Jason Gart and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is January 14, 2009, and we are in the offices of the National Institutes of Health in Bethesda,Maryland. Please state your full name and also spell it.

JH: John Allan Hanover, J-O-H-N—A-L-L-A-N—H-A-N-O-V-E-R.

JG: Thank you. Established in 1970, the Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, commonly known as LMB, currently has among its ten groups, four members of the National Academy of Sciences. LMB has trained many other prominent scientists and its research has contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history project to capture recollections of prominent scientists currently and formerly associated with the laboratory.

You were born in Oklahoma?

JH: Yes,Tulsa,Oklahoma.

JG: In what year?

JH: In 1953.

JG: Explain your family background. What did your parents do for a living?

JH: My father was a meat cutter, a butcher. My mother was a banker. Neither finished college. My father actually went to college briefly, but on a music scholarship because he played with the Tommy Dorsey Orchestra, for those of you who remember. He was a Dixieland and jazz musician, trombonist. My mother was working at a bank for many years, and also did not have the opportunity to attend college.

JG: What were some of your interests as a child?

JH: I was very interested in natural history, insects. I was interested in astronomy, particularly astronomy and imaging, photography. As I started moving through school, I became more interested in chemistry and physical sciences, and that is how I ended up in the biochemical arena.

JG: You went to the University of Tulsa, Oklahoma. Why did you decide to pursue biology?

JH: I believe the whole thing stems from a really excellent high school biology teacher at the Eliot School in Tulsa who just opened my eyes to the joy of biology. I had always been interested in natural history. I think the experimental sciences in the 1960s, fueled probably by Sputnik, were beginning to really take hold and there was a very strong intellectual flavor. The country was moving toward the physical sciences as a reasonable way to spend your life. I am not sure that is quite as true now but I remember thinking this is what I want to do and it was a great time. I wish I could remember the woman's name but I blanked on her name.

JG: What year did you graduate from high school?

JH: That would be 1970 or 1971.

JG: Do you have any brothers or sisters?

JH: I had an older brother who passed away from colon cancer at fifty-five. He was a college graduate in journalism and commercial art. My younger brother completed two years of college and is currently a meat cutter in Tulsa.

JG: When you entered biology what did you see yourself doing? Did you see yourself focusing on basic research?

JH: I was initially drawn to science education.

JG: Teaching at a university?

JH: Perhaps professor; but science education in the broader sense. I loved the popular treatments of science that I had read. I thought science education was very important. Once I entered graduate school at the University of Tulsa—I was in a Master's equivalent program in chemistry—I was told I had a talent for teaching. Then, when the career developed, it became financially impossible to become a teacher. I ended up doing research although I still teach quite a bit. I actually taught last night, four to six, in one of our classes.

JG: You attended the University of Tulsa and were in the biology department?

JH: I actually had a dual degree in biology and in chemistry and it was a master's equivalent. I was probably almost equally in the biology and chemistry departments.

JG: Talk about the training that you received in the department.

JH: Well, the University of Tulsa is and was, I think, a superb institution. It was extremely oriented toward the physical sciences. This is fueled in large part by petroleum engineering and chemical engineering, which is very strong there. These were serious courses. The biology courses were more in the natural history arena because this, after all, was before the dawn of what we now call modern biology. It was a very good grounding in both biology and chemistry. I had some very good teachers. The professor of molecular biology was a very influential person because he prompted my decision as to where to apply to graduate school, and then to work for the chairman of the department that I ended up actually attending when I went to graduate school.

JG: Reflect back to what the training was like for you at that time because it was almost a different type of science. Were there computers, mainframes?

JH: Training in the undergraduate arena . . . There really weren't even mainframes that we could access. In fact a big part of what was then physical science was learning how to program computers and use punch cards. If you wanted to run a program that you had written in order to analyze your data, for example, it would take two to three weeks just to troubleshoot it and then punch the cards again. Basically it was a nonstarter for a science student. I would say we were precomputational in that sense.

Most of the work in chemistry was done with slide rules and quite effectively. For the number of significant figures we needed this was perfectly appropriate. Probably still would be today. Training was focused more on conceptual training. The conceptual training in chemistry that I received was very physical and very mathematical as opposed to what I would eventually end up doing—which was biochemistry. This was really based very much on first principle. I look back on those days as very important because the quantitative approach to science was picked up in large part in those undergraduate days at the University of Tulsa.

JG: What prompted you to go to Johns Hopkins University?

JH: Well, as I mentioned, I had an undergraduate professor—unfortunately the names have escaped me at this point—who had worked for Albert L. Lehninger. Lehninger was one of the most influential instructors in biochemistry in the whole country and wrote what was probably the most widely used biochemistry text. My advisor in Tulsa said, "That is the place to learn biochemistry." I applied to numerous graduate programs, got into most of them, and ended up choosing the Johns Hopkins School of Medicine for graduate school.

JG: At that point you sought out a Ph.D. program?

JH: Actually, no. I applied to the MSTP program, and I got into the MSTP program, which was then called the M.D./Ph.D. program. My first year I was torn as to whether to complete the medical education during first year or two. In large part that was dictated by the fact that the projects were going so well in the Ph.D. part of the program that I hated to dilute my efforts to complete an M.D. that I thought I would never use. As it turned out I completed the first two basic science years in medical school, including the graduate courses which I was taking simultaneously, but never did complete the M.D. part of it.

JG: Did you have any interest in going the clinical route?

JH: No. Well, I could see myself going the clinical route but I think it would have been a disservice to myself. That was not my strength. Any talent that I bring to this is the ability to integrate multiple areas of research and put them together in a coherent whole. That would have been rewarding in medicine but probably not my calling. I sensed that even at the ripe old age of twenty-two or twenty-three when I had to make that decision.

JG: Speak about Dr. William J. Lennarz.

JH: Bill Lennarz was the mentor I eventually chose at Johns Hopkins. You could write books about Bill.

JG: He is a distinguished professor in the Department of Biochemistry and Cell Biology at Stony Brook University?

JH: He is at Stony Brook. He is still very active. He is a remarkable scientist, remarkable individual who had worked with Konrad E. Bloch, a Nobel Laureate. Bill was all business but an extremely warm and caring person. He ran his lab with incredible precision, I would say, and brought the best out of everyone who ever worked for him. It was a real pleasure to spend those five years with him. We just had a symposium in his honor three years ago in California and it was touching to hear people reminiscing; that is an oral history project in and of itself. When he was elected to the National Academy [of Sciences] we were all very gratified because his work really laid the groundwork for much of what we know now about how glycosylation reactions occur across the membrane. I was lucky enough to be involved in a lot of those studies. Bill has no bigger fan than me.

JG: Describe him as a scientist.

JH: He brought an intellectual rigor derived from his training in chemistry to a new area and that was biology. Even though he affectionately referred to the biologists as "those damn biologists" whom he recruited at the lab, he learned from them, and he embraced model systems long before that was in vogue. He had worked with the sea urchins, and he subsequently worked in yeast, and he embraced these things by bringing his rigor as a chemist to bear on each problem. I was impressed with that and it actually influenced me greatly when I started my own lab. I was not afraid to start model systems. Even today we continue to do chemistry alongside with forward genetics and modern biology. I think that was Bill's influence.

JG: What about the other people at John Hopkins. Who were your other mentors and some of the other people you interacted with?

JH: Well, I lived next door to a fellow named Burt Vogelstein, now a wellknown cancer researcher you may know about. I was a graduate student of Daniel DiMaio, now a well-known tumor virologist at Harvard. That includes Steve Bryant who wrote the CM3D instructional biology program used across the country. I would say that many of these folks out of that program have been successful. There were only seven graduates of the biochemistry, cell, and molecular biology program that year, and I think all of us survived. At the time, it was an extremely good place to train. The Ph.D. then was not the default if you could not get into medical school. The point I want to make is that the Ph.D. was really a conscious decision as opposed to a fallback position. Most of these people were superb, including the Ph.D./M.D. types. Stephen Desiderio, for example, is one of those who is doing very well. They were both good and a lot of fun; we had a good time in our years before we separated and did our own research.

In Bill Lennarz's lab there were a number of really excellent scientists. Gerald Hart, who is now chairman of that same department at Johns Hopkins, and I were close colleagues. We have worked on the same problem or some variant of it for twenty-five years, competing sometimes, collaborating other times. He is both a good friend and he is the one person I fear in the field I work in because he knows at least as much as I do, so it is fun. Gerry is one good guy.

Many others of Bill's trainees, have gone on to bigger and better things. I could mention John Lupus. I could mention some of Bill's subsequent colleagues, one of whom is now the deputy director of research at NORCA, who is over at Building 1.

JG: You came from Tulsa,Oklahoma. What was Baltimore like?

JH: This was 1976 or so when I first arrived in Baltimore. Baltimore at the time had just sort of gone through the throes of the late 1960s. There was sufficient remaining tension in the neighborhood to make it difficult for Hopkins to recruit faculty and there were some problems associated with that. But it was quite interesting for me.

JG: You get a postdoctoral fellowship at NIH?

JH: Yes.

JG: What did you know about NIH when you were at John Hopkins and how did you see it? What brought you to Ira Pastan's lab?

JH: I wanted to work on receptor-mediated endocytosis. I had decided that that was where my knowledge of carbohydrates and my knowledge of signaling could be best applied.

JG: This was the topic of your dissertation?

JH: My dissertation was on the transmembrane assembly of N-linked glycoproteins. I was very interested in how N-glycoproteins were assembled and the cell biology of that assembly process. How nucleotide sugars get across membranes and how that influences the assembly of N-linked glycoproteins. At the time, that was extremely timely because Gilbert Ashwell at the NIH had just discovered the asialoglycoprotein receptor, a carbohydrate based glycan. It was the first receptor identified. Ira was working on alpha 2-microglobulin receptor and had done a lot of the pioneer work on it. Elizabeth F. Neufeld, here at the NIH, had shown that there were carbohydrate-linked defects associated with some diseases—Sandhoff and Tay-Sachs. And Roscoe Brady had done work on Niemann-Pick disease, etc. This was really the center of the universe for receptor-mediated endocytosis. I also had an offer from the [Michael S.] Brown and [Joseph L.] Goldstein lab. They are superb. This was before they had won the Nobel Prize.

My decision was based largely on the fact that when I visited Ira Pastan's lab it seemed a lot more like Bill Lennarz's lab. It was broad. Ira was clearly a genius. He had assembled a very strong team and I felt that, in terms of training, I would do best at the NIH. I wrote a fellowship for the Jane Coffin Childs Memorial which came through. I believe it worked out very well and I would make the same decision again.

JG: Describe NIH in 1981.

JH: When I first came to the NIH from East Baltimore . . . I must admit that it was like a kid going into a candy store. I loved the green, the nature of the campus. There were tennis courts. It was also very accessible by car. It was wonderful. That became important because my wife and I were commuting from Columbia to split the difference between Baltimore and Washington. It was quite a place . . . really nice, open campus. It had a feeling of collegiality. It was smaller then in terms of the number of people and was very pleasant.

Scientifically it was quite different from what it is now, I believe. Research groups were typically smaller. There were a lot of ma and pa shops; individuals working with one or two people and a postdoc. Ira, however, had one of the larger labs at that time, but that appealed to me because I wanted to learn what was then—it is kind of laughable now—but was then in vogue, which was molecular biology, learning to work with nucleic acids. That was a training that I sought in this setting and did not get to experience in graduate school. It was the dawn of that era.

JG: How did you first meet Ira?

JH: When I interviewed in his lab in the fall of 1980. I visited his lab and made the decision that that is where I wanted to go. It was a very pleasant visit.

JG: How did Dr. Pastan explain the goals of his group?

JH: Well, when we sat down he described the work they were doing at the time on alpha 2-microglobulin and the mechanism of receptor mediated endocytosis. This is what intrigued me. He was doing many other things, but he focused on that. At the time, there were some very good people in the laboratory and I got to talk to many of them.

JG: That was the next question. Who is there and what are they working on?

JH: When I first visited, Jim [James H.] Keen was there, Bob [Robert B.] Dickson was there, Dick Schlagel was there. When I first visited, Nancy Rickert was there, and she was there subsequently as well. Fred [Frederick R.] Maxfield was in the lab and Fred and I got along very well. In fact, Fred and I attended a Gordon Research Conference together before I joined the lab, so I feel like we were contemporaries, although he preceded me by a few years. Jim Keen, who really started the work on clathrin in the laboratory, was just leaving; I believe I took Jim Keen's bench when I joined the lab. Bob Dickson and I sat across from one another and we were good friends until he passed away a couple years ago due to a heart attack. Takeshi Ito was in the lab at the time as was Jürgen Wehland, who had brought microinjection from Europe as a resource for the lab. It was a very exciting and stimulating place. There was a theory that Ira had suggested that transglutaminases might be involved in receptor mediated endocytosis. This really sort of set the field on fire because people thought of this as a pathway that could be modulated and I was very intrigued by that. I think that is when I decided that this was where I wanted to go.

JG: You are there on a postdoc for three or four years?

JH: I was there overall about four-and-a-half years. I worked first on the receptor mediated endocytosis pathway, worked on finding the receptor for alpha 2-microglobulin, a very nice project that was the basis of my fellowship proposal; several small papers were published. As an indication of how Ira worked at the time, and I think still does, Ira came in, we talked, and he said, "This looks good. We are completing this. I think we should start looking at another ligand. Let's look at transferrin." So I began to explore what was known about transferrin, an iron carrying protein now known to be involved in nearly everything. But certainly transferrin was the main mode of delivery of soluble iron in the body. I started looking into that in combination with Bob Dickson. Bob was working on the epidermal growth factor receptor and we wanted to compare and contrast the internalization pathway of those two. It worked out beautifully and I ended up publishing a paper with Bob in *PNAS* and another paper in *Cell*, sort of the major paper I contributed in Ira's lab at the time, defining the route of entry of transferrin and EGF [epidermal growth factor] and their movement through clathrin coated vesicles. It remains one of the papers I am proudest of. It does not get referenced as often as it might, but it really represents some of the very early biochemical contributions to the endocytic pathway.

JG: Describe Ira as a scientist and how he trained you as a young postdoc?

JH: Ira never let you rest on your laurels. I would say that he challenged everyone and kept them stimulated and he did it in quite a unique way. He would come in, just as an example, he will have played tennis with someone working on adenovirus, and he would say, "John, how do you think E1A works?" I think that is a direct quote from Ira. I hope he will correct me if I am wrong. [Laughs] I was petrified because I barely knew what it was, and now I am being asked how it worked. What one soon learned in working around Ira is that he read everything. It was very important to stay on your toes and to keep your level of intensity to at least a level as great as his.

People did not live in fear of Ira. They lived in awe of Ira because he seemed to be on top of all the scientific literature that we were all grappling with but he seemed to be two or three steps ahead of us. Very few scientists can make that claim. He was also very involved in the day-to-day science in the lab. People could barely keep one or two days ahead of Ira in terms of the data production. He would know the data and remember it at least as well as we did when it came to writing the paper. He is a remarkable scientist coming up with incredibly creative approaches to problems. To this day I remain in awe of Ira's ability to choose important problems and carry them through.

JG: Some of the people that I interviewed mentioned that he would work weekends and evenings. What do you think drove Ira?

JH: What drives all of us. Most scientists, at the level that we are talking about, are data junkies. It is not that they work to be famous. They work hard because they want to know that next answer. What really gives them pleasure is the excitement that comes from that next discovery. The data is what limits your ability to think about these things. Just like going to a really good meal and knowing there is a dessert at the end of it—you might rush through it just to get to the dessert. That's the way we are. We are very, very quick to get the data so that we can begin to think about it. The joy of science is getting there and being the first to think about the problem. It is a little bit like climbing a mountain and seeing the peak—at least imagining that you are the first one there. I am guessing that is what drives Ira and I am certain it drives me.

JG: Speak a moment about the clathrin work and your publication in *Cell*.

JH: That was an interesting mixture of what I would call cooperative thinking. I was very influenced by another scientist at the time, Jim [James] Rothman. I was a fan of Jim's work from my days in Bill's lab. We competed in Bill's lab, and then Jim also got interested in clathrin. He had developed a method whereby he could immunoabsorb clathrin containing vesicles. I decided to try that approach and I think that this was my decision to do this. Let's use that approach to look at the kinetics of endocytosis, a way of bringing kinetics into the picture. We had been following this thing morphologically, the work of Mark Willingham, who had some really gorgeous pictures, seeing these things entering an extension of pits. I wanted to see if we could look at this phenomenon biochemically and begin to dissect the process kinetically. I used Jim Rothman's technique and it worked beautifully. We learned something about not only that movement at the plasma membrane of proteins into the cell, but also at the level of where similar clathrin-coated pits are present. That turned out to be a lot of fun and Ira supported me in every piece of that.

It was also the beginning of my ability to think independently. I think it is fair to say that prior problems and work had been chosen and directed pretty much by Ira. Clathrin was when I felt I could spread my wings a bit. He was very supportive both on that work and the transferrin project. And then, of course, very supportive in my efforts to find a job. My first interview from Ira's lab, quite interestingly, was with Jim Rothman at Stanford [University]. He was a young faculty member and I went out there for my first seminar. They had asked Ira to recommend someone and he recommended me. I am sure I gave a dismally bad seminar but I had the chance because of people's respect for Ira.

JG: What were your aspirations at this time; in 1984-1985?

JH: In about 1984 I began to look for a job. I really wanted to continue the work that I had uncovered in Ira's lab, using cell fractionation with the antibody technique of Jim Rothman . . . I had used some tricks from graduate school and discovered that the nucleus had glycoproteins. Gerry Hart and I were sort of both looking at that problem. He had uncovered a protein modification called O-GlcNAc [O-linked N-acetylglucosamine] and I had shown, when I was in Ira's lab, with his permission, that O-GlcNAc is actually present in the nucleus. This is what I wanted to work on. I wanted to look at nuclear oscillation. The subject wasn't super well received, I have to say, when I gave my job seminar because they wanted someone working on receptor mediated endocytosis.

I should mention that toward the end of my stay in Ira's lab, I had asked to learn somatic cell genetics, and Ira's very, very good about that. If you ask to learn something . . . Of course, kids are fickle, they want to learn techniques. Ira is very good at saying, "Okay, but let's solve a problem." He put a paper on my desk by Victor Ling describing the protein P-glycoprotein, which was involved in permeability and asked me to purify it and make antibodies against it. We did that. That was really the start of the work on the permeability, glycoprotein which we now know to be MDR and the local drug resistance gene. I guess I was the first person in Ira's lab, I expect that he will correct me if I'm wrong, to begin to do the biochemistry. That was done in collaboration with Nancy Rickert and also Mr. Akiyama who was in the lab at the time. It was fun to get to learn some somatic cell genetics, a little molecular biology, and to continue working on glycoproteins. I also owe that one to Ira.

JG: By 1985 you had some notable scientific successes. What about some failures or disappointments. How did they impact you?

JH: There were some disappointments. I hate to call them failures but there were disappointments. I identified the LDL receptor in Ira's lab but could not purify it to homogeneity. We were actually beaten in terms of identifying the first receptor by the Brown and Goldstein group who purified the LDL [low density lipoprotein] receptor. On the other hand, that disappointment reinforced my belief that this was the way to go—biochemically—so I did pursue it. In collaboration with Tom August, just about when I was leaving Ira's lab, we identified a model clone for the receptor, that allowed others, [Dudley K.] Strickland and his people, to purify the receptors. Although I did not complete that project, I feel as if I played a major role in pushing it forward.

The job search was disappointing. I am sure this is disappointing for everyone but I keep letters of people saying, "This will never work," "This is absurd," "This guy is crazy," all of the above. I have letters for all that. It was extremely disappointing because the one thing that I had learned in both Bill' s and Ira's lab was that creativity matters. When I got on the job market, I realized that, although creativity matters, you better keep it to yourself until you get that job. [Laughs] I expect that this is not a unique disappointment.

JG: Talk about the style of the lab. Papers were discussed by the whole group and each week there were discussion groups and things like that?

JH: There were lab meetings. Those lab meetings were typically data exchange meetings where we would sit around and talk about the data. We would show the primary data. We would discuss problems with the data as we had obtained it. Ira's role in much of that was to be supportive. He also expressed his ideas about what the findings might mean, but he was very good—I think very fair—about letting people come up with their own notions of what the data meant. In fact, he asked, "What do you think it means?" It is something that I immediately embraced as a good way to mentor because, before you start imposing your own ideas on people, you owe it to students to let them express their own thoughts. It is a very, very good training exercise and that was a big part of what Ira did in those meetings. They were fairly open meetings but not benign. If someone was clearly not working hard enough, it became clear, not only because of Ira's actions but also the reactions of the group. There was peer pressure at those meetings.

JG: You go to the Laboratory of Biochemistry and Metabolism at the NIDDK. You mentioned that you were looking at other jobs?

JH: Yes. I had a couple of job offers actually, I should say. I had a job at M. D. Anderson [Cancer Center] in Texas, that was quite good. I also had one at Albert Einstein College of Medicine, that was good. Ira, frankly, had a major role in helping me get this job at the NIH. His friend and colleague, Bill [William B.] Jakoby and him produced a volume *Methods in Enzymology* on tissue culture together, and was actually running one of the very first tenured track searches at the NIH. Tenure track searches I think probably started about the same era, about 1983 or 1984; it was an attempt to pick the best available people by advertising the job. Bill had started such a search in this Institute with one of Ira's friends, Jesse Roth, who was the scientific director of Intramural Research at the time. Basically Ira arranged to have me meet with Bill and give a seminar, and they liked what they heard, and so Bill and Jesse hired me. I owe this job almost exclusively to Ira and his support during those years. Even though I had other offers, he certainly was instrumental in making me choose this job.

JG: In 1996, speaking about calmodulin-driven pathway, you wrote, "[t]he finding was unexpected, controversial, and admittedly not well accepted following its publication." I thought that was a fascinating statement. What brought this about?

JH: When I moved to this Institute, I decided to take everything I had learned from both experiences, Bill Lennarz's and Ira's, and start something new. That was a bit heroic because, quite frankly, I had many good things going while in Ira's lab and could have completed any of them, including the work on the MDR in my new job. Ira had suggested that I actually continue work on that. I probably should have listened to him, but didn't. I decided that I was going to follow my ambition to look at the nuclear glycoproteins, which we did. The result of that was first published in 1986 or 1987 where we showed that the glycosylated proteins were principally restricted to the nuclear pore complex and that other nuclear glycoproteins were present. We started studying nuclear entry and nuclear import, a very productive period until about 1994 or so. At that time Tom Schweitzer joined the lab, and we began studies showing that calmodulin was a key regulator of nuclear transport.

At the time, we and others had discovered that another protein, Ran, was involved in the nuclear import. Almost the entire field, with the exception of our lab, focused on the Ran pathway. We decided, being a little bit of a contrarian I guess, that this was not where I wanted to go. I thought calmodulin was the more interesting mediator because calcium mobilization was an intrinsic part of all cell activation. So that is where I proceeded. We wrote the paper for *PNAS* which Gil [G. Gilbert] Ashwell actually submitted to *PNAS*. I thought it would be a big splash paper. Alas, it sort of went nowhere in the first few years. People would laugh at meetings, questioning its validity because it did not fit the dogma. Almost ten years later, it became clear that human patients were subject to diseases due to binding sites for calmodulin that did not allow the protein SRY to enter the nucleus. Male sex determination requires that a protein called SRY, represented on the Y chromosome, came with the nucleus. They did not know how it occurred. That really broke open that field.

We just completed a review in the *Journal of Biological Chemistry* which explains a lot of that, but it was a very exciting time, and we knew we were correct. We just did not know what the implications of the binding were. Frankly, the stamina to stand those years and to continue the work derived entirely from Bill Lennarz and Ira, whose basic approach was to go with the data no matter what people say. You present the data and it could be wrong at times, but you stick to your guns. Both of them taught that lesson.

JG: You have 135 publications or about that. Talk about the role of citations today in science. Do you feel you have the ability to spend five years studying something and not produce a publication?

JH: A very good question. For me, it is one of the principal symptoms of the problems that are associated with the way science is now done. Unfortunately, I was trained by Bill to do science that was complete, and that meant making sure that you had tested, in every way you knew how, to prove you were wrong. The goal was to prove not that your theories are correct. The goal was to prove that your theory was incorrect and to try every way you could to prove that you were wrong; that takes longer than to do one or two experiments to prove you are correct.

What has happened in science, and it is not necessarily a bad thing, is that there are many ideas that are put forth that are, to put it terribly, half-baked. Half-baked ideas, while on the surface can be benign, or appear to be benign, are actually destructive because they cause people to waste a lot of time, effort, and money. I have tried to avoid that where I could.

I think that we publish a lot for a group of our size. We are productive. But I am very happy to say that we have never had to really retract or change any of our central views because we have been very careful, and we continue to be very careful. That derives not only from my work with Bill Lennarz who was extremely careful, but also my work with Ira who thought it was important to not mislead people and present the data in a concise and thorough way. I really believe that my training in those two laboratories allowed me to avoid that storm.

Of course, publication styles differ from individual to individual. We have always published fairly large, perhaps too long, manuscripts but they are well cited. I guess we do well by modern indices, the so-called *h*-index and all of that. I am not sure I believe that those things are necessarily useful. If you pull up Ira's *h*-index, and I have done it just for fun, it is huge. It is enormous. But that is a reflection of Ira's high productivity and his creativity. It is a very rare combination. I am actually quite proud of my publication record because I know that the papers that we have published are sound and that we have misled no one.

JG: There are people like Michel Morange who argue that there are projects you avoid. A postdoc or young researcher, who doesn't have tenure, quickly realizes that there are areas with no funding or money. Pursuing these topics can affect one's job and employment opportunities.

JH: It's a very good point. Many people are afraid to follow their ambition because they believe that it will not support their career sufficiently to allow them to survive and I guess that is to put it as succinctly as I can. I was aware of the problem. We have always maintained a sort of bread-and-butter project in addition to some fairly zany ideas that go along with it. We have been able to maintain a productive laboratory and still ask what I consider high-risk, high-impact questions. I think you have to find a way of doing that. People do it in various ways and Ira is one of the best at it that I have seen. He paid the bill, so to say, but he was also extremely creative in thinking outside the box. I have tried to pattern my lab after that. At least two of the projects we are currently working on are extremely, I would say, high risk, and yet I feel we have to do that. I feel like I am in a position in which I can do that in the intramural program at the NIH, and I know that it is one of the things that makes the intramural program unique. It's true that the atmosphere is changing; the science citation *h*-index type analysis is used when we sit on the central tenure committee, for example. Approaches to science are changing. I am not sure necessarily it is for the better, but I think all investigators, at some stage in their career, have had to deal with changes in approach.

JG: How about selecting dissertation topics? Do you think that there is an emphasis with picking a subject that is in a high impact area?

JH: Definitely. People seem to choose areas that are in vogue. I mean that this has been the era of genomics, whole genome approaches and systems biology. Many people are drawn to that. I think that has always been true, that people tend toward the vogue because that's where the money is. New investigators face a very long dormancy period before they can start their own laboratories. I believe that the receipt age of the average RO1 grant has gone up to close to age forty. That lag is slowing progress because I would say people are most creative, certainly in the physical sciences, at a younger age. You would hate to see increasing displacement between the age of creativity and the funding of that creativity.

We have to think about ways of changing that. We do have ways, but there are many people who do not fall under the RO1 blanket, who are funded through other mechanisms and other relationships. Research associates and extramural staff scientists here at the NIH are an example. I think we need to do more to promote those people. I think it is a very disturbing trend and big science plays a big part of that.

JG: What about responsibilities to younger scientists? How do you balance the need for skepticism of data and then also creativity?

JH: I suspect that my mentoring style is a combination of Bill Lennarz's and Ira Pastan's. While I can't sit down and tell you which derives from which, I certainly choose problems in a manner very similar to the way that Ira chose them. I try to think five years ahead, try to think of what will be important five years from now, what we should be studying rather than what we are studying. And yet I try to bring a kind of physical science rigor to the way the science is done. That derives, in large part, from Bill's influence. I am willing to challenge conclusions at a meeting. I say, "Why do you believe that?" "Do you have evidence to suggest that's true?" Not in a mean way, but in a probing way. I believe that Ira continues to do things in a similar way.

We owe it to the young people who come to the NIH, or come to any institution seeking training and knowledge, to keep them excited and I try to do nothing to dampen their excitement. If they are excited about a problem I tend to let them pursue it, always making sure that they have a safety net. They may want to do "recombineering" or some fairly high-risk genomic project. That makes me think of my own failures, not being able to complete the purification of the receptor, for example, that taught me that ambition can sometimes exceed one's capabilities. I try to make sure that they have a safety net in the lab.

JG: Talk about the health of science today. We have had the mapping of the human genome and other advancements but are there greater funding constraints nowadays? What is the health of the field?

JH: It depends of course on the field. I would say modern biology, if you want to think of it broadly, is in a true renaissance. There are so many resources, so much data available to the thinking mind, that it is hard not to do good science. That may not sound right but there are so many ideas percolating that if you are not excited, you have just got to do something else. Every day I get to work seven in the morning anxious to read what my colleagues have written; I can't wait to get in the lab myself and I do that at least a couple days a week to test some of my own ideas. If you are not excited by it . . .

The availability afforded by the Web of raw data and people's analysis of that data is just enormous. We used to grab the *Journal of Biological Chemistry*, the JBC, one of the premier journals at the time, and you could read the thing cover to cover and know most of what your colleagues and most of what will be discussed for the next month because, in fact, it was all in that one place. That is no longer even close to true. The number of publications online and throughout the Web is so large that it is a challenge to keep up with the science. Big science fuels lots of science. The interface between information technology, bioinformatics and biology, in particular, has just allowed a tremendous blurring of fields. There is no such thing as biochemistry or cell biology or molecular biology or bacteriology. They are all intertwined. Of course, that makes training a challenge.

JG: How do you balance both your professional and family responsibilities? The amount of hours that scientists log is really extraordinary.

JH: I actually believe scientists learn to do that just as they are learning the other skills. I think Ira . . . I alluded to the fact that he had come back from a tennis match. I do not want to give you the impression that Ira did nothing but play tennis. I believe he used that as a kind of intellectual stimulation. It was not just that he was playing with intelligent colleagues. It was also that he realized that people need to take a break. I have actually patterned myself after that for many years. I take an exercise break almost everyday for an hour, hour-and-a-half. They all know that I'm going. I either do tai chi or I run or I lift weights. I think that such breaks are very important for mental health and I encourage my postdocs to do the same.

The balance with life has been difficult for both my wife and I. Both of us are scientists. We have had to make trade-offs. I suspect part of the productivity equation in both cases was influenced by . . . We have two children who are now in college. That was very hard to get through those child-rearing years and I am sure that my science suffered. I don't regret a bit of that because it was an important part of my life. Nevertheless it is a problem that impacts women disproportionately and certainly did in my wife's case. It impacted both of us, but I think the societal impact is greater on women than men. She is now a very successful program officer in NIDDK. We weathered the storm but I would never underestimate what a big challenge that is for scientific families. It has a huge impact.

JG: How about women generally in the sciences? Is it different now than it was in the 1980s?

JH: I hate to venture into that arena; it is an awkward thing. When I was a graduate student there were women, many of them single, who were interested in science. Very dedicated. You saw very few married women with children in science. That has changed dramatically over the years and now we run family friendly labs. It is fair to say that most of us think that is a healthy trend. There is no way that that was sustainable—this sort of old boys' network, old girls' network to some extent too. The women who were there were dedicated but they couldn't really support their family life in parallel with their scientific aspirations. That was very difficult . . . I would say the transition occurred in the late 1980s with improvement since then.

JG: What are you currently working on?

JH: Currently we are working on two problems. The calmodulin-dependent nuclear import pathway that I discussed and, what I believe may prove to be our major discovery, at least in my limited period, the relationship between nutrient sensing and innate immunity. In particular this OGlcNAc pathway I have been mentioning appears to transcriptionally, and in terms of signaling pathways, impact the innate immune system. Many of the diseases we study—diabetes, myelitis, Alzheimer's disease, and diseases of inflammation—have always been thought of as metabolic disorders. Genomics is telling us that innate immunity is the function that is regulated by the O-GlcNAc sensing pathway. We are trying to understand, with some success, the relationship between the several nutrient sensing pathways and innate immunity. It is an epigenetic modification of prolitain, for example, that we have observed. I think this will probably end up being my major accomplishment in the next decade or so that I have left to do active science. I am hoping that' s the case.

JG: You mentioned your hobbies. You are an amateur astronomer?

JH: Yes. I am an amateur astronomer and avid photographer. A lot of sports activities, tennis, and music. Folk musician. I play a lot of folk instruments, always have. That was a very fun time in Ira's lab. Most of us were products of the 1960s and 1970s. Nearly everyone there was interested in the same kind of music, stemming from Pete Seeger and Bob Dylan, and I continued that interest. The amateur astronomy is an outlet for my teaching ambitions because I do a lot of outreach for children, letting them look through the telescopes, and explaining what they see. It is great fun which I do that on a regular basis.

JG: Last question. If you have one piece of advice, one lesson learned that you would like to pass on to a future scientist operating in ten or twenty years in the future, what would it be?

JH: That is to stick to your data; believe your data. Go where your data leads you. A friend of mine sent me this quote from [Ivan] Pavlov, who speaks to this very thing. I will just read this. "What would I wish for the youth of my fatherland who devote themselves to science?" Same kind of question. His final comment here is one that I find poignant. "Third, passion. Remember, science requires your whole life. Even if you had two lives to give, it would still not be enough. Science demands of man effort and supreme passion. Be passionate in your work and in your quests." It is a variation of what I tried to express earlier. I think that if you do not enjoy coming in every day, if it is not the driving passion of your life, you really are doing yourself a disservice. You should do something else so you can put those passions to work on. A lot of my postdoc's decide they want to do policy rather than work in a lab. I support that because they have made a conscious decision. You can't say, "You do not want to do that. You are a good scientist." I think you have to support their instincts. Follow your data, follow your instincts.

JG: Thank you very much.

JH: Thank you, sir.

[End of interview]